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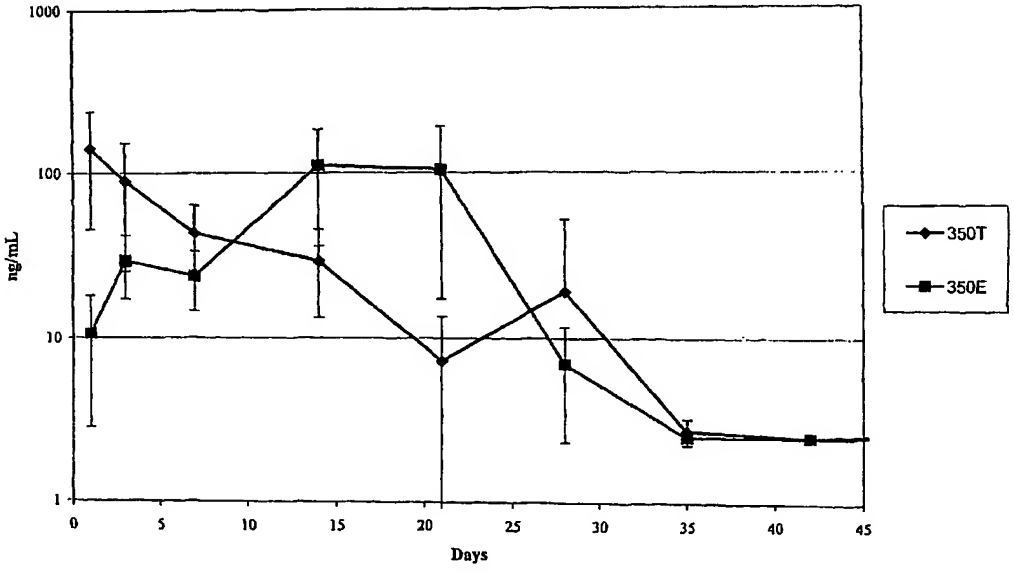

(57) Abstract: The invention provides biodegradable implants sized for implantation in an ocular region and methods for treating medical conditions of the eye. The implants are formed from a mixture of hydrophilic end and hydrophobic end PLGA, and deliver active agents into an ocular region without a high burst release.

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BIODEGRADABLE OCULAR IMPLANT

FIELD OF THE INVENTION

[0001] The present invention relates to the field of ophthalmology. In particular, biodegradable implants and methods for treating medical conditions of the eye are provided.

BACKGROUND OF THE INVENTION

[0002] Immunosuppressive agents are routinely used for the treatment of uveitis of various etiologies. For example, topical or oral glucocorticoids are often included in the therapeutic regimen; however, a major problem with these routes of administration is the inability to achieve an adequate intraocular drug concentration of the glucocorticoid. In fact, the difficulties of treating uveitis due to poor intraocular penetration of topical medications into the posterior segment is well known (Bloch-Michel E. (1992). "Opening address: intermediate uveitis," In Intermediate Uveitis, Dev. Ophthalmol. W.R.F. Böke et al. eds., Basel: Karger, 23:1-2; Pinar, V. Intermediate uveitis. Massachusetts Eye & Ear Infirmary Immunology Service at <http://www.immunology.meei.harvard.edu/imed.htm> (visited in 1998); Rao, N.A. et al. (1997). "Intraocular inflammation and uveitis," In Basic and Clinical Science Course. Section 9 (1997-1998) San Francisco: American Academy of Ophthalmology, pp. 57-80, 102-103, 152-156; Böke, W. (1992). "Clinical picture of intermediate uveitis," In Intermediate Uveitis, Dev. Ophthalmol. W.R.F. Böke et al. eds., Basel: Karger, 23:20-7; and Cheng C-K et al. (1995). "Intravitreal sustained-release dexamethasone device in the treatment of experimental uveitis," Invest. Ophthalmol. Vis. Sci. 36:442-53).

[0003] Systemic glucocorticoid administration may be used alone or in addition to topical glucocorticoids for the treatment of uveitis. Prolonged exposure to high plasma concentrations (administration of 1 mg/kg/day for 2-3 weeks) of steroid is often necessary so that therapeutic levels can be achieved in the eye (Pinar, V.

"Intermediate uveitis," Massachusetts Eye & Ear Infirmary Immunology Service at <http://www.immunology.meei.harvard.edu/imed.htm> (visited in 1998)).

[0004] However, these high drug plasma levels commonly lead to systemic side effects such as hypertension, hyperglycemia, increased susceptibility to infection, peptic ulcers, psychosis, and other complications (Cheng C-K et al. (1995). "Intravitreal sustained-release dexamethasone device in the treatment of experimental uveitis," Invest. Ophthalmol. Vis. Sci. 36:442-53; Schwartz, B. (1966). "The response of ocular pressure to corticosteroids," Ophthalmol. Clin. North Am. 6:929-89; Skalka, H.W. et al. (1980). "Effect of corticosteroids on cataract formation," Arch Ophthalmol 98:1773-7; and Renfro, L. et al. (1992). "Ocular effects of topical and systemic steroids," Dermatologic Clinics 10:505-12).

[0005] In addition, overall drug delivery to the eye may be poor for drugs with short plasma half-lives since their exposure to intraocular tissues is limited. Therefore, the most efficient way of delivering a drug to the posterior segment is to place it directly into the vitreous (Maurice, D.M. (1983). "Micropharmaceutics of the eye," Ocular Inflammation Ther. 1:97-102; Lee, V.H.L. et al. (1989). "Drug delivery to the posterior segment" Chapter 25 In Retina. T.E. Ogden and A.P. Schachat eds., St. Louis: CV Mosby, Vol. 1, pp. 483-98; and Olsen, T.W. et al. (1995). "Human scleral permeability: effects of age, cryotherapy, transscleral diode laser, and surgical thinning," Invest. Ophthalmol. Vis. Sci. 36:1893-1903).

[0006] Techniques such as intravitreal injection have shown promising results, but due to the short intraocular half-life of glucocorticoids (approximately 3 hours), intravitreal injections must be repeated to maintain drug levels. In turn, this repetitive process increases the potential for side effects such as retinal detachment, endophthalmitis, and cataracts (Maurice, D.M. (1983). "Micropharmaceutics of the eye," Ocular Inflammation Ther. 1:97-102; Olsen, T.W. et al. (1995). "Human scleral permeability: effects of age, cryotherapy, transscleral diode laser, and surgical thinning," Invest. Ophthalmol. Vis. Sci. 36:1893-1903; and Kwak, H.W. and

D'Amico, D. J. (1992). "Evaluation of the retinal toxicity and pharmacokinetics of dexamethasone after intravitreal injection," Arch. Ophthalmol. 110:259-66).

[0007] One of the alternatives to intravitreal injection to administer drugs is the placement of biodegradable implants under the sclera or into the subconjunctival or suprachoroidal space, as described in U.S. 4,863,457 to Lee; WO 95/13765 to Wong et al.; WO 00/37056 to Wong et al.; EP 430,539 to Wong; in Gould et al., *Can. J. Ophthalmol.* 29(4):168-171 (1994); and in Apel et al., *Curr. Eye Res.* 14:659-667 (1995).

[0008] Furthermore, the controlled release of drugs from polylactide/polyglycolide (PLGA) copolymers into the vitreous has been disclosed, e.g., in U.S. 5,501,856 to Ohtori et al. and EP 654,256 to Ogura.

[0009] Recent experimental work has demonstrated that uncapped PLGA degrades faster than capped (end-capped) PLGA (Park et al., *J. Control. Rel.* 55:181-191 (1998); Tracy et al., *Biomaterials* 20:1057-1062 (1999); and Jong et al., *Polymer* 42:2795-2802 (2001). Accordingly, implants containing mixtures of uncapped and capped PLGA have been formed to modulate drug release. For example, U.S. 6,217,911 to Vaughn et al. ('911) and U.S. 6,309,669 to Setterstrom et al. ('669) disclose the delivery of drugs from a blend of uncapped and capped PLGA copolymer to curtail initial burst release of the drugs. In the '911 patent, the composition delivers non-steroidal anti-inflammatory drugs from PLGA microspheres made by a solvent extraction process or PLGA microcapsules prepared by a solvent evaporation process over a duration of 24 hours to 2 months. In the '669 patent, the composition delivers various pharmaceuticals from PLGA microcapsules over a duration of 1-100 days. The PLGA microspheres or microcapsules are administered orally or as an aqueous injectable formulation. As mentioned above, there is poor partitioning of drug into the eye with oral administration. Furthermore, use of an aqueous injectable drug composition (for injecting into the eye) should be avoided since the eye is a closed space (limited volume) with intraocular pressure

ranges that are strictly maintained. Administration of an injectable may increase intraocular volume to a point where intraocular pressures would then become pathologic.

[0010] Consequently, a biodegradable implant for delivering a therapeutic agent to an ocular region may provide significant medical benefit for patients afflicted with a medical condition of the eye.

SUMMARY OF THE INVENTION

[0011] The biodegradable implants and methods of this invention are typically used to treat medical conditions of the eye. Consequently, the implants are sized such that they are appropriate for implantation in the intended ocular region.

[0012] In one variation, the bioerodible implant for treating medical conditions of the eye includes an active agent dispersed within a biodegradable polymer matrix, wherein the bioerodible implant has an *in vivo* in rabbit eye cumulative release profile in which less than about 15 percent of the active agent is released about one day after implantation of the bioerodible implant and greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant, and wherein the biodegradable polymer matrix comprises a mixture of hydrophilic end group PLGA and hydrophobic end group PLGA.

[0013] In another variation, the bioerodible implant for treating medical conditions of the eye includes an active agent dispersed within a biodegradable polymer matrix, wherein the bioerodible implant is formed by an extrusion method, and wherein the bioerodible implant has an *in vivo* in rabbit eye cumulative release profile in which greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant.

[0014] In a further variation, the bioerodible implant for treating medical conditions of the eye includes an active agent dispersed within a biodegradable polymer matrix,

wherein the bioerodible implant exhibits a cumulative release profile in which greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant, and wherein the cumulative release profile is approximately sigmoidal in shape over about 28 days after implantation.

[0015] In yet a further variation, the bioerodible implant for treating medical conditions of the eye includes an active agent dispersed within a biodegradable polymer matrix, wherein the biodegradable polymer matrix comprises a mixture of PLGA having hydrophilic end groups and PLGA having hydrophobic end groups. Examples of hydrophilic end groups include, but are not limited to, carboxyl, hydroxyl, and polyethylene glycol. Examples of hydrophobic end groups include, but are not limited to, alkyl esters and aromatic esters.

[0016] In yet another variation, the bioerodible implant for treating medical conditions of the eye includes an active agent dispersed within a biodegradable polymer matrix, wherein the bioerodible implant has an *in vivo* in rabbit eye cumulative release profile in which less than about 15 percent of the active agent is released about one day after implantation of the bioerodible implant and greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant.

[0017] Various active agents may be incorporated into the bioerodible implants. In one variation, anti-inflammatory agents, including, but not limited to nonsteroidal anti-inflammatory agents and steroidal anti-inflammatory agents may be used. In another variation, active agents that may be used in the bioerodible implants are ace-inhibitors, endogenous cytokines, agents that influence basement membrane, agents that influence the growth of endothelial cells, adrenergic agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, antibacterials, antihypertensives, pressors, antiprotozoal agents, antiviral agents, antifungal agents, anti-infective agents, antitumor agents, antimetabolites, and antiangiogenic agents.

[0018] The implants may be used to treat medical conditions of the eye in mammalian subjects, e.g., human subjects. Examples of such medical conditions include, but are not limited to, uveitis, macular edema, macular degeneration, retinal detachment, ocular tumors, fungal or viral infections, multifocal choroiditis, diabetic retinopathy, proliferative vitreoretinopathy (PVR), sympathetic opthalmia, Vogt Koyanagi-Harada (VKH) syndrome, histoplasmosis, uveal diffusion, vascular occlusion, and the like.

[0019] Furthermore, upon implantation in an ocular region of the subject, the bioerodible implants deliver the active agent such that the resulting concentration of active agent *in vivo* in rabbit aqueous humor is approximately 10-fold less than in rabbit vitreous humor. The active agent is delivered so that a therapeutic amount of active agent is provided in the ocular region of interest. In general, the therapeutic amount of active agent in an ocular region may be modified by varying the size of the bioerodible implant.

BRIEF DESCRIPTION OF THE OF THE DRAWINGS

[0020] Figure 1 shows the *in vivo* concentration of dexamethasone in the vitreous of rabbit eyes over a 42 day period after implantation of compressed and extruded biodegradable implants containing 350 μg dexamethasone into the posterior segment of rabbit eyes .

[0021] Figure 2 shows the *in vivo* cumulative percentage release of dexamethasone in the vitreous of rabbit eyes over a 42 day period after implantation of compressed and extruded biodegradable implants containing 350 μg dexamethasone and 700 μg dexamethasone into the posterior segment of rabbit eyes.

[0022] Figure 3 shows the *in vivo* concentration of dexamethasone in the aqueous humor of rabbit eyes over a 42 day period after implantation of compressed and

extruded biodegradable implants containing 350 μg dexamethasone into the posterior segment of rabbit eyes.

[0023] Figure 4 shows the *in vivo* concentration of dexamethasone in the plasma (from a rabbit blood sample) over a 42 day period after implantation of compressed and extruded biodegradable implants containing 350 μg dexamethasone into the posterior segment of rabbit eyes.

[0024] Figure 5 shows the *in vivo* concentration of dexamethasone in the vitreous of rabbit eyes over a 42 day period after implantation of compressed and extruded biodegradable implants containing 700 μg dexamethasone into the posterior segment of rabbit eyes.

[0025] Figure 6 shows the *in vivo* concentration of dexamethasone in the aqueous humor of rabbit eyes over a 42 day period after implantation of compressed and extruded biodegradable implants containing 700 μg dexamethasone into the posterior segment of rabbit eyes.

[0026] Figure 7 shows the *in vivo* concentration of dexamethasone in the plasma (from a rabbit blood sample) over a 42 day period after implantation of compressed and extruded biodegradable implants containing 700 μg dexamethasone into the posterior segment of rabbit eyes.

[0027] Figure 8 shows the *in vivo* concentration of dexamethasone in the vitreous of rabbit eyes over a 42 day period after implantation of compressed and extruded biodegradable implants containing 350 μg dexamethasone and 700 μg dexamethasone into the posterior segment of rabbit eyes.

[0028] Figure 9 shows the *in vitro* total cumulative percentage release of dexamethasone into a saline solution at 37°C from 60/40 w/w dexamethasone/PLGA implants having a weight ratio of 40:0 hydrophobic end to hydrophilic end PLGA

(312-140-2), weight ratio of 30:10 hydrophobic end to hydrophilic end PLGA (312-140-4), weight ratio of 20:20 hydrophobic end to hydrophilic end PLGA (312-140-3), and weight ratio of 0:40 hydrophobic end to hydrophilic end PLGA (312-140-1).

[0029] Figure 10 compares the *in vitro* cumulative percentage release of dexamethasone into a saline solution at 37°C for six lots of extruded implants having 60% by weight dexamethasone, 30% by weight hydrophilic end PLGA, and 10% by weight hydrophobic end PLGA.

DETAILED DESCRIPTION OF THE INVENTION

[0030] The present invention provides biodegradable ocular implants and methods for treating medical conditions of the eye. Usually, the implants are formed to be monolithic, i.e., the particles of active agent are distributed throughout the biodegradable polymer matrix. Furthermore, the implants are formed to release an active agent into an ocular region of the eye over various time periods. The active agent may be release over a time period including, but is not limited to, approximately six months, approximately three months, approximately one month, or less than one month.

Definitions

[0031] For the purposes of this description, we use the following terms as defined in this section, unless the context of the word indicates a different meaning.

[0032] As used herein, the term "ocular region" refers generally to any area of the eyeball, including the anterior and posterior segment of the eye, and which generally includes, but is not limited to, any functional (e.g., for vision) or structural tissues found in the eyeball, or tissues or cellular layers that partly or completely line the interior or exterior of the eyeball. Specific examples of areas of the eyeball in an ocular region include the anterior chamber, the posterior chamber, the vitreous cavity, the choroid, the suprachoroidal space, the conjunctiva, the subconjunctival space, the

episcleral space, the intracorneal space, the epicorneal space, the sclera, the pars plana, surgically-induced avascular regions, the macula, and the retina.

[0033] By "subject" it is meant mammalian subjects, preferably humans. Mammals include, but are not limited to, primates, farm animals, sport animals, e.g., horses (including race horses), cats, dogs, rabbits, mice, and rats.

[0034] As used herein, the term "treat" or "treating" or "treatment" refers to the resolution, reduction, or prevention of a medical condition of the eye or the sequelae of a medical condition of the eye.

[0035] As used herein, the terms "active agent" and "drug" are used interchangeably and refer to any substance used to treat a medical condition of the eye.

[0036] As used herein, the term "medical condition" refers to conditions that are generally treated non-invasively, e.g., with drugs, as well as conditions that are generally treated using a surgical procedure.

[0037] By "therapeutic amount" it is meant a concentration of active agent that has been locally delivered to an ocular region that is appropriate to safely treat a medical condition of the eye.

[0038] As used herein, the term "cumulative release profile" refers to the cumulative total percent of agent released from the implant either into the posterior segment *in vivo* in rabbit eyes over time or into the specific release medium *in vitro* over time.

Biodegradable Implants For Treating Medical Conditions of the Eye

[0039] The implants of the invention include an active agent dispersed within a biodegradable polymer. The implant compositions typically vary according to the preferred drug release profile, the particular active agent used, the condition being treated, and the medical history of the patient. Active agents that may be used

include, but are not limited to, ace-inhibitors, endogenous cytokines, agents that influence basement membrane, agents that influence the growth of endothelial cells, adrenergic agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, anti-inflammatory agents, antihypertensives, pressors, antibacterials, antivirals, antifungals, antiprotozoals, anti-infectives, antitumor agents, antimetabolites, and antiangiogenic agents.

[0040] In one variation the active agent is methotrexate. In another variation, the active agent is retinoic acid. In a preferred variation, the anti-inflammatory agent is a nonsteroidal anti-inflammatory agent. Nonsteroidal anti-inflammatory agents that may be used include, but are not limited to, aspirin, diclofenac, flurbiprofen, ibuprofen, ketorolac, naproxen, and suprofen. In a more preferred variation, the anti-inflammatory agent is a steroidal anti-inflammatory agent.

Steroidal Anti-Inflammatory Agents

[0041] The steroidal anti-inflammatory agents that may be used in the ocular implants include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and any of their derivatives.

[0042] In one variation, cortisone, dexamethasone, fluocinolone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone, and their derivatives, are preferred steroidal anti-inflammatory agents. In another preferred variation, the steroidal anti-inflammatory agent is dexamethasone. In another variation, the biodegradable implant includes a combination of two or more steroidal anti-inflammatory agents.

[0043] The steroidal anti-inflammatory agent may constitute from about 10% to about 90% by weight of the implant. In one variation, the agent is from about 40% to about 80% by weight of the implant. In a preferred variation, the agent comprises about 60% by weight of the implant.

The Biodegradable Polymer Matrix

[0044] In one variation, the active agent may be homogeneously dispersed in the biodegradable polymer matrix of the implants. The selection of the biodegradable polymer matrix to be employed will vary with the desired release kinetics, patient tolerance, the nature of the disease to be treated, and the like. Polymer characteristics that are considered include, but are not limited to, the biocompatibility and biodegradability at the site of implantation, compatibility with the active agent of interest, and processing temperatures. The biodegradable polymer matrix usually comprises at least about 10, at least about 20, at least about 30, at least about 40, at least about 50, at least about 60, at least about 70, at least about 80, or at least about 90 weight percent of the implant. In one variation, the biodegradable polymer matrix comprises about 40% by weight of the implant.

[0045] Biodegradable polymer matrices which may be employed include, but are not limited to, polymers made of monomers such as organic esters or ethers, which when degraded result in physiologically acceptable degradation products. Anhydrides, amides, orthoesters, or the like, by themselves or in combination with other monomers, may also be used. The polymers are generally condensation polymers.

The polymers may be crosslinked or non-crosslinked. If crosslinked, they are usually not more than lightly crosslinked, and are less than 5% crosslinked, usually less than 1% crosslinked.

[0046] For the most part, besides carbon and hydrogen, the polymers will include oxygen and nitrogen, particularly oxygen. The oxygen may be present as oxy, e.g., hydroxy or ether, carbonyl, e.g., non-oxo-carbonyl, such as carboxylic acid ester, and the like. The nitrogen may be present as amide, cyano, and amino. An exemplary list of biodegradable polymers that may be used are described in Heller, Biodegradable Polymers in Controlled Drug Delivery, In: "CRC Critical Reviews in Therapeutic Drug Carrier Systems", Vol. 1. CRC Press, Boca Raton, FL (1987).

[0047] Of particular interest are polymers of hydroxyaliphatic carboxylic acids, either homo- or copolymers, and polysaccharides. Included among the polyesters of interest are homo- or copolymers of D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, caprolactone, and combinations thereof. Copolymers of glycolic and lactic acid are of particular interest, where the rate of biodegradation is controlled by the ratio of glycolic to lactic acid. The percent of each monomer in poly(lactic-co-glycolic)acid (PLGA) copolymer may be 0-100%, about 15-85%, about 25-75%, or about 35-65%. In a preferred variation, a 50/50 PLGA copolymer is used . More preferably, a random copolymer of 50/50 PLGA is used.

[0048] Biodegradable polymer matrices that include mixtures of hydrophilic and hydrophobic ended PLGA may also be employed, and are useful in modulating polymer matrix degradation rates. Hydrophobic ended (also referred to as capped or end-capped) PLGA has an ester linkage hydrophobic in nature at the polymer terminus. Typical hydrophobic end groups include, but are not limited to alkyl esters and aromatic esters. Hydrophilic ended (also referred to as uncapped) PLGA has an end group hydrophilic in nature at the polymer terminus. PLGA with a hydrophilic end groups at the polymer terminus degrades faster than hydrophobic ended PLGA because it takes up water and undergoes hydrolysis at a faster rate (Tracy et al.,

Biomaterials 20:1057-1062 (1999)). Examples of suitable hydrophilic end groups that may be incorporated to enhance hydrolysis include, but are not limited to, carboxyl, hydroxyl, and polyethylene glycol. The specific end group will typically result from the initiator employed in the polymerization process. For example, if the initiator is water or carboxylic acid, the resulting end groups will be carboxyl and hydroxyl. Similarly, if the initiator is a monofunctional alcohol, the resulting end groups will be ester or hydroxyl.

[0049] The implants may be formed from all hydrophilic end PLGA or all hydrophobic end PLGA. In general, however, the ratio of hydrophilic end to hydrophobic end PLGA in the biodegradable polymer matrices of this invention range from about 10:1 to about 1:10 by weight. For example, the ratio may be 3:1, 2:1, or 1:1 by weight. In a preferred variation, an implant with a ratio of hydrophilic end to hydrophobic end PLGA of 3:1 w/w is used.

Additional Agents

[0050] Other agents may be employed in the formulation for a variety of purposes. For example, buffering agents and preservatives may be employed. Preservatives which may be used include, but are not limited to, sodium bisulfite, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric nitrate, methylparaben, polyvinyl alcohol and phenylethyl alcohol. Examples of buffering agents that may be employed include, but are not limited to, sodium carbonate, sodium borate, sodium phosphate, sodium acetate, sodium bicarbonate, and the like, as approved by the FDA for the desired route of administration. Electrolytes such as sodium chloride and potassium chloride may also be included in the formulation.

[0051] The biodegradable ocular implants may also include additional hydrophilic or hydrophobic compounds that accelerate or retard release of the active agent. Furthermore, the inventors believe that because hydrophilic end PLGA has a higher degradation rate than hydrophobic end PLGA due to its ability to take up water more

readily, increasing the amount of hydrophilic end PLGA in the implant polymer matrix will result in faster dissolution rates. Figure 9 shows that the time from implantation to significant release of active agent (lag time) increases with decreasing amounts of hydrophilic end PLGA in the ocular implant. In Figure 9, the lag time for implants having 0% hydrophilic end PLGA (40% w/w hydrophobic end) was shown to be about 21 days. In comparison, a significant reduction in lag time was seen with implants having 10% w/w and 20% w/w hydrophilic end PLGA.

Release Kinetics

[0052] The inventors believe the implants of the invention are formulated with particles of an active agent dispersed within a biodegradable polymer matrix. Without being bound by theory, the inventors believe that release of the active agent is achieved by erosion of the biodegradable polymer matrix and by diffusion of the particulate agent into an ocular fluid, e.g., the vitreous, with subsequent dissolution of the polymer matrix and release of the active agent. The inventors believe that the factors that influence the release kinetics include such characteristics as the size of the active agent particles, the solubility of the active agent, the ratio of active agent to polymer(s), the method of manufacture, the surface area exposed, and the erosion rate of the polymer(s). The release kinetics achieved by this form of active agent release are different than that achieved through formulations which release active agents through polymer swelling, such as with crosslinked hydrogels. In that case, the active agent is not released through polymer erosion, but through polymer swelling, which releases agent as liquid diffuses through the pathways exposed.

[0053] The inventors believe that the release rate of the active agent depends at least in part on the rate of degradation of the polymer backbone component or components making up the biodegradable polymer matrix. For example, condensation polymers may be degraded by hydrolysis (among other mechanisms) and therefore any change in the composition of the implant that enhances water uptake by the implant will likely increase the rate of hydrolysis, thereby increasing the rate of polymer degradation and erosion, and thus increasing the rate of active agent release.

[0054] The release kinetics of the implants of the invention are dependent in part on the surface area of the implants. A larger surface area exposes more polymer and active agent to ocular fluid, causing faster erosion of the polymer matrix and dissolution of the active agent particles in the fluid. The size and shape of the implant may also be used to control the rate of release, period of treatment, and active agent concentration at the site of implantation. At equal active agent loads, larger implants will deliver a proportionately larger dose, but depending on the surface to mass ratio, may possess a slower release rate. For implantation in an ocular region, the total weight of the implant preferably ranges, e.g., from about 100-5000 μg, usually from about 500-1500 μg. In one variation, the total weight of the implant is about 600 μg. In another variation, the total weight of the implant is about 1200 μg.

[0055] The bioerodible implants are typically solid, and may be formed as particles, sheets, patches, plaques, films, discs, fibers, rods, and the like, or may be of any size or shape compatible with the selected site of implantation, as long as the implants have the desired release kinetics and deliver an amount of active agent that is therapeutic for the intended medical condition of the eye. The upper limit for the implant size will be determined by factors such as the desired release kinetics, toleration for the implant at the site of implantation, size limitations on insertion, and ease of handling. For example, the vitreous chamber is able to accommodate relatively large rod-shaped implants, generally having diameters of about 0.05 mm to 3 mm and a length of about 0.5 to about 10 mm. In one variation, the rods have diameters of about 0.1 mm to about 1 mm. In another variation, the rods have diameters of about 0.3 mm to about 0.75 mm. In yet a further variation, other implants having variable geometries but approximately similar volumes may also be used.

[0056] As previously discussed, the release of an active agent from a biodegradable polymer matrix may also be modulated by varying the ratio of hydrophilic end PLGA to hydrophobic end PLGA in the matrix. Release rates may be further

manipulated by the method used to manufacture the implant. For instance, as illustrated in Examples 4-7, extruded 60/40 w/w dexamethasone/PLGA implants having a ratio of hydrophilic end and hydrophobic end PLGA of 3:1, compared to compressed tablet implants, demonstrate a different drug release profile and concentration of agent in the vitreous over about a one month period. Overall, a lower burst of agent release and a more consistent level of agent in the vitreous is demonstrated with the extruded implants.

[0057] As shown in Figure 2 and Examples 4 and 5, a higher initial burst of active agent release occurs on day one after implantation with the 350 μg dexamethasone compressed tablet implant (350T) in comparison to the 350 μg dexamethasone extruded implant (350E). A higher initial burst of active agent release also occurs with the 700 μg dexamethasone compressed implant (700T) in comparison to the 700 μg dexamethasone extruded implant (700E) on day 1, as shown in Figure 2 and Examples 6 and 7.

[0058] The proportions of active agent, biodegradable polymer matrix, and any other additives may be empirically determined by formulating several implants with varying proportions and determining the release profile *in vitro* or *in vivo*. A USP approved method for dissolution or release test can be used to measure the rate of release *in vitro* (USP 24; NF 19 (2000) pp. 1941-1951). For example, a weighed sample of the implant is added to a measured volume of a solution containing 0.9% NaCl in water, where the solution volume will be such that the active agent concentration after release is less than 20% of saturation. The mixture is maintained at 37°C and stirred or shaken slowly to maintain the implants in suspension. The release of the dissolved active agent as a function of time may then be followed by various methods known in the art, such as spectrophotometrically, HPLC, mass spectroscopy, and the like, until the solution concentration becomes constant or until greater than 90% of the active agent has been released.

[0059] In one variation, the extruded implants described herewith (ratio of hydrophilic end PLGA to hydrophobic end PLGA of 3:1) may have *in vivo* cumulative percentage release profiles with the following described characteristics, as shown in Figure 2, where the release profiles are for release of the active agent *in vivo* after implantation of the implants into the vitreous of rabbit eyes. The volume of rabbit eyes is approximately 60-70% of human eyes.

[0060] At day one after implantation, the percentage *in vivo* cumulative release may be between about 0% and about 15%, and more usually between about 0% and about 10%. At day one after implantation, the percentage *in vivo* cumulative release may be less than about 15%, and more usually less than about 10%.

[0061] At day three after implantation, the percentage *in vivo* cumulative release may be between about 0% and about 20%, and more usually between about 5% and about 15%. At day three after implantation, the percentage *in vivo* cumulative release may be less than about 20%, and more usually less than about 15%.

[0062] At day seven after implantation, the percentage *in vivo* cumulative release may be between about 0% and about 35%, more usually between about 5% and about 30%, and more usually still between about 10% and about 25%. At day seven after implantation, the percentage *in vivo* cumulative release may be greater than about 2%, more usually greater than about 5%, and more usually still greater than about 10%.

[0063] At day fourteen after implantation, the percentage *in vivo* cumulative release may be between about 20% and about 60%, more usually between about 25% and about 55%, and more usually still between about 30% and about 50%. At day fourteen after implantation, the percentage *in vivo* cumulative release may be greater than about 20%, more usually greater than about 25%, and more usually still greater than about 30%.

[0064] At day twenty-one after implantation, the percentage *in vivo* cumulative release may be between about 55% and about 95%, more usually between about 60% and about 90%, and more usually still between about 65% and about 85%. At day twenty-one after implantation, the percentage *in vivo* cumulative release may be greater than about 55% , more usually greater than about 60% , and more usually still greater than about 65%.

[0065] At day twenty-eight after implantation, the percentage *in vivo* cumulative release may be between about 80% and about 100%, more usually between about 85% and about 100%, and more usually still between about 90% and about 100%. At day twenty-eight after implantation, the percentage *in vivo* cumulative release may be greater than about 80%, more usually greater than about 85%, and more usually still greater than about 90%.

[0066] At day thirty-five after implantation, the percentage *in vivo* cumulative release may be between about 95% and about 100%, and more usually between about 97% and about 100%. At day thirty-five after implantation, the percentage *in vivo* cumulative release may be greater than about 95%, and more usually greater than about 97%.

[0067] In one variation, the percentage *in vivo* cumulative release has the following characteristics: one day after implantation it is less than about 15%; three days after implantation it is less than about 20%; seven days after implantation it is greater than about 5%; fourteen days after implantation it is greater than about 25%; twenty-one days after implantation it is greater than about 60%; and twenty-eight days after implantation it is greater than about 80%. In another variation, the percentage *in vivo* cumulative release has the following characteristics: one day after implantation it is less than about 10%; three days after implantation it is less than about 15%; seven days after implantation it is greater than about 10%; fourteen days after implantation it is greater than about 30%; twenty-one days after implantation it is

greater than about 65%; twenty-eight days after implantation it is greater than about 85%.

[0068] In yet another variation, the extruded implants described in this patent may have *in vitro* cumulative percentage release profiles in saline solution at 37°C with the following characteristics, as further described below, and as shown in Figure 10.

[0069] The percentage *in vitro* cumulative release at day one may be between about 0% and about 5%, and more usually between about 0% and about 3%. The percentage *in vitro* cumulative release at day one may be less than about 5%, and more usually less than about 3%.

[0070] The percentage *in vitro* cumulative release at day four may be between about 0% and about 7%, and more usually between about 0% and about 5%. The percentage *in vitro* cumulative release at day four may be less than about 7%, and more usually less than about 5%.

[0071] The percentage *in vitro* cumulative release at day seven may be between about 1% and about 10%, and more usually between about 2% and about 8%. The percentage *in vitro* cumulative release at day seven may be greater than about 1%, and more usually greater than about 2%.

[0072] The percentage *in vitro* cumulative release at day 14 may be between about 25% and about 65%, more usually between about 30% and about 60%, and more usually still between about 35% and about 55%. The percentage *in vitro* cumulative release at day 14 may be greater than about 25%, more usually greater than about 30%, and more usually still greater than about 35%.

[0073] The percentage *in vitro* cumulative release at day 21 may be between about 60% and about 100%, more usually between about 65% and about 95%, and more usually still between about 70% and about 90%. The percentage *in vitro* cumulative

release at day 21 may be greater than about 60%, more usually greater than about 65%, and more usually still greater than about 70%.

[0074] The percentage *in vitro* cumulative release at day 28 may be between about 75% and about 100%, more usually between about 80% and about 100%, and more usually still between about 85% and about 95%. The percentage *in vitro* cumulative release at day 28 may be greater than about 75%, more usually greater than about 80%, and more usually still greater than about 85%.

[0075] The percentage *in vitro* cumulative release at day 35 may be between about 85% and about 100%, more usually between about 90% and about 100%, and more usually still between about 95% and about 100%. The percentage *in vitro* cumulative release at day 35 may be greater than about 85%, more usually greater than about 90%, and more usually still greater than about 95%.

[0076] In one variation, the percentage *in vitro* cumulative release has the following characteristics: after one day it is less than about 1%; after four days it is less than about 7%; after seven days it is greater than about 2%; after 14 days it is greater than about 30%; after 21 days it is greater than about 65%; after 28 days it is greater than about 80%; and after 35 days it is greater than about 90%. In another variation, the percentage *in vitro* cumulative release has the following characteristics: after one day it is less than about 3%; after four days it is less than about 5%; after seven days it is greater than about 2%; after 14 days it is greater than about 35%; after 21 days it is greater than about 70%; after 28 days it is greater than about 85%; and after 35 days it is greater than about 90%.

[0077] Besides showing a lower burst effect for the extruded implants, Figures 2 and 10 also demonstrate that after 28 days *in vivo* in rabbit eyes, or *in vitro* in a saline solution at 37°C, respectively, almost all of the active agent has been released from the implants. Furthermore, Figures 2 and 10 show that the active agent release profiles for the extruded implants *in vivo* (from the time of implantation) and *in vitro*

(from the time of placement into a saline solution at 37°C) are substantially similar and follow approximately a sigmoidal curve, releasing substantially all of the active agent over 28 days. From day one to approximately day 17, the curves show approximately an upward curvature (i.e., the derivative of the curve increases as time increases), and from approximately day 17 onwards the curves show approximately a downward curvature (i.e., the derivative of the curve decreases as time increases).

[0078] In contrast, the plots shown in Figure 2 for the 350 μg and 700 μg dexamethasone compressed tablet implants exhibit a higher initial burst of agent release generally followed by a gradual increase in release. Furthermore, as shown in Figures 1 and 5, implantation of a compressed implant results in different concentrations of active agent in the vitreous at various time points from implants that have been extruded. For example, as shown in Figures 1 and 5, with extruded implants there is a gradual increase, plateau, and gradual decrease in intravitreal agent concentrations. In contrast, for compressed tablet implants, there is a higher initial active agent release followed by an approximately constant decrease over time. Consequently, the intravitreal concentration curve for extruded implants results in more sustained levels of active agent in the ocular region.

[0079] In addition to the previously described implants releasing substantially all of the therapeutic agent within 35 days, by varying implant components including, but not limited to, the composition of the biodegradable polymer matrix, implants may also be formulated to release a therapeutic agent for any desirable duration of time, for example, for about one week, for about two weeks, for about three weeks, for about four weeks, for about five weeks, for about six weeks, for about seven weeks, for about eight weeks, for about nine weeks, for about ten weeks, for about eleven weeks, for about twelve weeks, or for more than 12 weeks.

[0080] Another important feature of the extruded implants is that different concentration levels of active agent may be established in the vitreous using different doses of the active agent. As illustrated in Figure 8, the concentration of agent in the

vitreous is significantly larger with the 700 μg dexamethasone extruded implant than with the 350 μg dexamethasone extruded implant. Different active agent concentrations are not demonstrated with the compressed tablet implant. Thus, by using an extruded implant, it is possible to more easily control the concentration of active agent in the vitreous. In particular, specific dose-response relationships may be established since the implants can be sized to deliver a predetermined amount of active agent.

Applications

[0081] Examples of medical conditions of the eye which may be treated by the implants and methods of the invention include, but are not limited to, uveitis, macular edema, macular degeneration, retinal detachment, ocular tumors, fungal or viral infections, multifocal choroiditis, diabetic retinopathy, proliferative vitreoretinopathy (PVR), sympathetic opthalmia, Vogt Koyanagi-Harada (VKH) syndrome, histoplasmosis, uveal diffusion, and vascular occlusion. In one variation, the implants are particularly useful in treating such medical conditions as uveitis, macular edema, vascular occlusive conditions, proliferative vitreoretinopathy (PVR), and various other retinopathies.

Method of Implantation

[0082] The biodegradable implants may be inserted into the eye by a variety of methods, including placement by forceps, by trocar, or by other types of applicators, after making an incision in the sclera. In some instances, a trocar or applicator may be used without creating an incision. In a preferred variation, a hand held applicator is used to insert one or more biodegradable implants into the eye. The hand held applicator typically comprises an 18-30 GA stainless steel needle, a lever, an actuator, and a plunger.

[0083] The method of implantation generally first involves accessing the target area within the ocular region with the needle. Once within the target area, e.g., the vitreous cavity, the lever on the hand held device is depressed to cause the actuator to

drive the plunger forward. As the plunger moves forward, it pushes the implant into the target area.

Extrusion Methods

[0084] The use of extrusion methods allows for large-scale manufacture of implants and results in implants with a homogeneous dispersion of the drug within the polymer matrix. When using extrusion methods, the polymers and active agents that are chosen are stable at temperatures required for manufacturing, usually at least about 50°C. Extrusion methods use temperatures of about 25°C to about 150°C, more preferably about 60°C to about 130°C.

[0085] Different extrusion methods may yield implants with different characteristics, including but not limited to the homogeneity of the dispersion of the active agent within the polymer matrix. For example, using a piston extruder, a single screw extruder, and a twin screw extruder will generally produce implants with progressively more homogeneous dispersion of the active. When using one extrusion method, extrusion parameters such as temperature, extrusion speed, die geometry, and die surface finish will have an effect on the release profile of the implants produced.

[0086] In one variation of producing implants by extrusion methods, the drug and polymer are first mixed at room temperature and then heated to a temperature range of about 60°C to about 150°C, more usually to about 130°C for a time period of about 0 to about 1 hour, more usually from about 0 to about 30 minutes, more usually still from about 5 minutes to about 15 minutes, and most usually for about 10 minutes. The implants are then extruded at a temperature of about 60°C to about 130°C, preferably at a temperature of about 75°C.

[0087] In a preferred extrusion method, the powder blend of active agent and PLGA is added to a single or twin screw extruder preset at a temperature of about 80°C to about 130°C, and directly extruded as a filament or rod with minimal residence time

in the extruder. The extruded filament or rod is then cut into small implants having the loading dose of active agent appropriate to treat the medical condition of its intended use.

EXAMPLES

[0088] The following examples serve to more fully describe the manner of using the above-described invention. It is understood that these examples in no way serve to limit the scope of this invention, but rather are presented for illustrative purposes.

EXAMPLE 1

Manufacture of Compressed Tablet Implants

[0089] Micronized dexamethasone (Pharmacia, Peapack, NJ) and micronized hydrophobic end 50/50 PLGA (Birmingham Polymers, Inc., Birmingham, AL) were accurately weighed and placed in a stainless steel mixing vessel. The vessel was sealed, placed on a Turbula mixer and mixed at a prescribed intensity, e.g., 96 rpm, and time, e.g., 15 minutes. The resulting powder blend was loaded one unit dose at a time into a single-cavity tablet press. The press was activated at a pre-set pressure, e.g., 25 psi, and duration, e.g., 6 seconds, and the tablet was formed and ejected from the press at room temperature. The ratio of dexamethasone to PLGA was 70/30 w/w for all compressed tablet implants.

EXAMPLE 2

Manufacture of Extruded Implants

[0090] Micronized dexamethasone (Pharmacia, Peapack, NJ) and unmicronized PLGA were accurately weighed and placed in a stainless steel mixing vessel. The vessel was sealed, placed on a Turbula mixer and mixed at a prescribed intensity, e.g., 96 rpm, and time, e.g., 10-15 minutes. The unmicronized PLGA composition comprised a 30/10 w/w mixture of hydrophilic end PLGA (Boehringer Ingelheim, Wallingford, CT) and hydrophobic end PLGA (Boehringer Ingelheim, Wallingford, CT). The resulting powder blend was fed into a DACA Microcompounder-Extruder (DACA, Goleta, CA) and subjected to a pre-set temperature, e.g., 115°C, and screw

speed, e.g., 12 rpm. The filament was extruded into a guide mechanism and cut into exact lengths that corresponded to the designated implant weight. The ratio of dexamethasone to total PLGA (hydrophilic and hydrophobic end) was 60/40 w/w for all extruded implants.

EXAMPLE 3

Method for Placing Implants Into the Vitreous

[0091] Implants were placed into the posterior segment of the right eye of New Zealand White Rabbits by incising the conjunctiva and sclera between the 10 and 12 o'clock positions with a 20-gauge microvitreoretinal (MVR) blade. Fifty to 100 μL of vitreous humor was removed with a 1-cc syringe fitted with a 27-gauge needle. A sterile trocar, preloaded with the appropriate implant (drug delivery system, DDS), was inserted 5 mm through the sclerotomy, and then retracted with the push wire in place, leaving the implant in the posterior segment. Sclerae and conjunctivae were than closed using a 7-0 Vicryl suture.

EXAMPLE 4

In vivo Release of Dexamethasone From 350μg Dexamethasone Compressed Tablet Implants

[0092] Example 4 demonstrates the high initial release but generally lower intravitreal concentration of dexamethasone from compressed tablet implants as compared to extruded implants. The 350μg compressed tablet implant (350T) was placed in the right eye of New Zealand White Rabbits as described in Example 3. Vitreous samples were taken periodically and assayed by LC/MS/MS to determine *in vivo* dexamethasone delivery performance. As seen in Figure 1, dexamethasone reached detectable mean intravitreal concentrations from day 1 (142.20 ng/ml) through day 35 (2.72 ng/ml), and the intravitreal concentration of dexamethasone gradually decreased over time.

[0093] In addition to the vitreous samples, aqueous humor and plasma samples were also taken. The 350T showed a gradual decrease in aqueous humor dexamethasone

concentrations over time, exhibiting a detectable mean dexamethasone aqueous humor concentration at day 1 (14.88 ng/ml) through day 21 (3.07 ng/ml), as demonstrated in Figure 3. The levels of dexamethasone in the aqueous humor strongly correlated with the levels of dexamethasone in the vitreous humor, but at a much lower level (approximately 10-fold lower). Figure 4 shows that only trace amounts of dexamethasone was found in the plasma.

EXAMPLE 5

In vivo Release of Dexamethasone From 350µg Dexamethasone Extruded Implants

[0094] Example 5 demonstrates the lower initial release and generally more sustained intravitreal concentration of dexamethasone from extruded implants. The 350µg extruded implant (350E) was placed in the right eye of New Zealand White Rabbits as described in Example 3. Vitreous samples were taken periodically and assayed by LC/MS/MS to determine *in vivo* dexamethasone delivery performance. Referring to Figure 1, 350E showed detectable mean vitreous humor concentrations on day 1 (10.66 ng/ml) through day 28 (6.99 ng/ml). The 350T implant had statistically significant higher dexamethasone concentrations on day 1 ($p=0.037$) while the 350E had a statistically significant higher dexamethasone level on day 21 ($p=0.041$).

[0095] In addition to the vitreous samples, aqueous humor and plasma samples were also taken. In Figure 3 , the 350E showed detectable mean dexamethasone aqueous humor concentrations at day 1 (6.67 ng/ml) through day 42 (2.58 ng/ml) with the exception of day 35 in which the values were below the quantification limit. On the whole, the levels of dexamethasone in the aqueous strongly correlated with the levels of dexamethasone in the vitreous humor, but at a much lower level (approximately 10-fold lower). Figure 4 demonstrates that only a trace amount of dexamethasone was found in the plasma.

EXAMPLE 6

In vivo Release of Dexamethasone From 700µg Dexamethasone Compressed Tablet Implants

[0096] Example 6 also shows the high initial release and generally lower intravitreal concentration of dexamethasone from compressed tablet implants. The 700µg compressed tablet dosage form (700T) was placed in the right eye of New Zealand White Rabbits as described in Example 3. Vitreous samples were taken periodically and assayed by LC/MS/MS to determine *in vivo* dexamethasone delivery performance. As seen in Figure 5, the 700T reached detectable mean dexamethasone vitreous humor concentrations at day 1 (198.56 ng/ml) through day 42 (2.89 ng/ml), and a gradual decrease in the intravitreal dexamethasone concentration over time.

[0097] In addition to the vitreous samples, aqueous humor and plasma samples were also obtained. As seen in Figure 6, the 700T exhibited a gradual decrease in aqueous humor dexamethasone concentrations over time, and reached detectable mean dexamethasone aqueous humor concentrations at day 1 (25.90 ng/ml) through day 42 (2.64 ng/ml) with the exception of day 35 in which the values were below the quantification limit. The levels of dexamethasone in the aqueous humor strongly correlated with the levels of dexamethasone in the vitreous humor, but at a much lower level (approximately 10-fold lower). Figure 7 demonstrates that only a trace amount of dexamethasone was found in the plasma.

EXAMPLE 7

In vivo Release of Dexamethasone From 700µg Dexamethasone Extruded Implants

[0098] Example 7 also illustrates the lower initial release and generally higher intravitreal concentration of dexamethasone from extruded implants. The 700µg extruded implant (700E) was placed in the right eye of New Zealand White Rabbits as described in Example 3. Vitreous samples were taken periodically and assayed by LC/MS/MS to determine *in vivo* dexamethasone delivery performance. As seen in Figure 5, the 700E had a mean detectable vitreous humor concentration of dexamethasone from day 1 (52.63 ng/ml) through day 28 (119.70 ng/ml).

[0099] In addition to the vitreous samples, aqueous humor and plasma samples were also taken. As seen in Figure 6, the 700E reached a detectable mean aqueous humor

concentration on day 1 (5.04 ng/ml) through day 28 (5.93 ng/ml). The levels of dexamethasone in the aqueous strongly correlated with the levels of dexamethasone in the vitreous humor, but at a much lower level (approximately 10-fold lower). Figure 7 demonstrates that only a trace amount of dexamethasone was found in the plasma.

* * *

[0100] All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent, or patent application were specifically and individually indicated to be so incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit and scope of the appended claims.

CLAIMS

1. A bioerodible implant for treating a medical condition of the eye comprising an active agent dispersed within a biodegradable polymer matrix, wherein the bioerodible implant has an *in vivo* in rabbit eye cumulative release profile in which less than about 15 percent of the active agent is released about one day after implantation of the bioerodible implant and greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant, and wherein the biodegradable polymer matrix comprises a mixture of hydrophilic end group PLGA and hydrophobic end group PLGA.

2. The bioerodible implant of claim 1 wherein the active agent is selected from the group consisting of ace-inhibitors, endogenous cytokines, agents that influence basement membrane, agents that influence the growth of endothelial cells, adrenergic agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, anti-inflammatory agents, antihypertensives, pressors, antibacterials, antivirals, antifungals, antiprotozoals, anti-infective agents, antitumor agents, antimetabolites, and antiangiogenic agents.

3. The bioerodible implant of claim 1 wherein the active agent comprises an anti-inflammatory agent or any derivative thereof.

4. The bioerodible implant of claim 1 wherein the active agent comprises a steroidal anti-inflammatory agent or any derivative thereof.

5. The bioerodible implant of claim 4 wherein the active agent is selected from the group consisting of cortisone, dexamethasone, fluocinolone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and any derivative thereof.

6. The bioerodible implant of claim 4 wherein the active agent comprises dexamethasone.

7. The bioerodible implant of claim 1 wherein the implant is sized for implantation in an ocular region.

8. The bioerodible implant of claim 7 wherein the ocular region is selected from the group consisting of the anterior chamber, the posterior chamber, the vitreous cavity, the choroid, the suprachoroidal space, the conjunctiva, the subconjunctival space, the episcleral space, the intracorneal space, the epicorneal space, the sclera, the pars plana, surgically-induced avascular regions, the macula, and the retina.

9. The bioerodible implant of claim 7 wherein the ocular region is the vitreous cavity.

10. A bioerodible implant for treating a medical condition of the eye comprising an active agent dispersed within a biodegradable polymer matrix, wherein the bioerodible implant is formed by an extrusion method, and wherein the bioerodible implant has an *in vivo* in rabbit eye cumulative release profile in which greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant.

11. The bioerodible implant of claim 10 wherein the active agent is selected from the group consisting of ace-inhibitors, endogenous cytokines, agents that influence basement membrane, agents that influence the growth of endothelial cells, adrenergic agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, anti-inflammatory agents, antihypertensives, pressors, antibacterials, antivirals, antifungals, antiprotozoals, anti-infective agents, antitumor agents, antimetabolites, and antiangiogenic agents.

12. The bioerodible implant of claim 10 wherein the active agent comprises an anti-inflammatory agent or any derivative thereof.

13. The bioerodible implant of claim 10 wherein the active agent comprises a steroidal anti-inflammatory agent or any derivative thereof.

14. The bioerodible implant of claim 13 wherein the active agent is selected from the group consisting of cortisone, dexamethasone, fluocinolone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and any derivative thereof.

15. The bioerodible implant of claim 13 wherein the active agent comprises dexamethasone.

16. The bioerodible implant of claim 10 wherein the active agent is about 10 to about 90 percent by weight of the bioerodible implant.

17. The bioerodible implant of claim 16 wherein the active agent is about 60 percent by weight of the bioerodible implant.

18. The bioerodible implant of claim 10 wherein the biodegradable polymer matrix comprises a polyester.

19. The bioerodible implant of claim 18 wherein the biodegradable polymer matrix comprises poly(lactic-co-glycolic)acid (PLGA) copolymer.

20. The bioerodible implant of claim 19 wherein the ratio of lactic to glycolic acid monomers is about 50/50 weight percentage.

21. The bioerodible implant of claim 19 wherein the PLGA copolymer is about 20 to about 90 weight percent of the bioerodible implant.

22. The bioerodible implant of claim 21 wherein the PLGA copolymer is about 40 percent by weight of the bioerodible implant.

23. The bioerodible implant of claim 10 wherein the implant is sized for implantation in an ocular region.

24. The bioerodible implant of claim 23 wherein the ocular region is selected from the group consisting of the anterior chamber, the posterior chamber, the vitreous cavity, the choroid, the suprachoroidal space, the conjunctiva, the subconjunctival space, the episcleral space, the intracorneal space, the epicorneal space, the sclera, the pars plana, surgically-induced avascular regions, the macula, and the retina.

25. The bioerodible implant of claim 23 wherein the ocular region is the vitreous cavity.

26. A bioerodible implant for treating a medical condition of the eye comprising an active agent dispersed within a biodegradable polymer matrix, wherein the bioerodible implant exhibits a cumulative release profile in which greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant, and wherein the cumulative release profile is approximately sigmoidal in shape over about 28 days after implantation.

27. The bioerodible implant of claim 26 wherein the cumulative release profile is an *in vivo* in rabbit eye cumulative release profile.

28. The bioerodible implant of claim 26 wherein the cumulative release profile is an *in vitro* cumulative release profile.

29. The bioerodible implant of claim 26 wherein the active agent is selected from the group consisting of ace-inhibitors, endogenous cytokines, agents that influence

basement membrane, agents that influence the growth of endothelial cells, adrenergic agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, anti-inflammatory agents, antihypertensives, pressors, antibacterials, antivirals, antifungals, antiprotozoals, anti-infective agents, antitumor agents, antimetabolites, and antiangiogenic agents.

30. The bioerodible implant of claim 26 wherein the active agent comprises an anti-inflammatory agent or any derivative thereof.

31. The bioerodible implant of claim 26 wherein the active agent comprises a steroidal anti-inflammatory agent or any derivative thereof.

32. The bioerodible implant of claim 31 wherein the active agent is selected from the group consisting of cortisone, dexamethasone, fluocinolone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and any derivative thereof.

33. The bioerodible implant of claim 31 wherein the active agent comprises dexamethasone.

34. The bioerodible implant of claim 26 wherein the active agent is about 10 to about 90 percent by weight of the bioerodible implant.

35. The bioerodible implant of claim 34 wherein the active agent is about 60 percent by weight of the bioerodible implant.

36. The bioerodible implant of claim 26 wherein the biodegradable polymer matrix comprises a polyester.

37. The bioerodible implant of claim 36 wherein the biodegradable polymer matrix comprises poly(lactic-co-glycolic)acid (PLGA) copolymer.

38. The bioerodible implant of claim 37 wherein the ratio of lactic to glycolic acid monomers is about 50/50 weight percentage.

39. The bioerodible implant of claim 37 wherein the PLGA copolymer is about 20 to about 90 weight percent of the bioerodible implant.

40. The bioerodible implant of claim 39 wherein the PLGA copolymer is about 40 percent by weight of the bioerodible implant.

41. The bioerodible implant of claim 26 wherein the implant is sized for implantation in an ocular region.

42. The bioerodible implant of claim 41 wherein the ocular region is selected from the group consisting of the anterior chamber, the posterior chamber, the vitreous cavity, the choroid, the suprachoroidal space, the conjunctiva, the subconjunctival space, the episcleral space, the intracorneal space, the epicorneal space, the sclera, the pars plana, surgically-induced avascular regions, the macula, and the retina.

43. The bioerodible implant of claim 41 wherein the ocular region is the vitreous cavity.

44. A bioerodible implant for treating a medical condition of the eye comprising an active agent dispersed within a biodegradable polymer matrix, wherein the biodegradable polymer matrix comprises a mixture of PLGA having hydrophilic end groups and PLGA having hydrophobic end groups, and wherein the bioerodible implant is sized for implantation in an ocular region.

45. The bioerodible implant of claim 44 wherein the active agent is selected from the group consisting of ace-inhibitors, endogenous cytokines, agents that influence basement membrane, agents that influence the growth of endothelial cells, adrenergic

agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, anti-inflammatory agents, antihypertensives, pressors, antibacterials, antivirals, antifungals, antiprotozoals, anti-infective agents, antitumor agents, antimetabolites, and antiangiogenic agents.

46. The bioerodible implant of claim 44 wherein the active agent comprises an anti-inflammatory agent or any derivative thereof.

47. The bioerodible implant of claim 44 wherein the active agent comprises a steroidal anti-inflammatory agent or any derivative thereof.

48. The bioerodible implant of claim 47 wherein the active agent is selected from the group consisting of cortisone, dexamethasone, fluocinolone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and any derivative thereof.

49. The bioerodible implant of claim 47 wherein the active agent comprises dexamethasone.

50. The bioerodible implant of claim 44 wherein the active agent is about 10 to about 90 percent by weight of the bioerodible implant.

51. The bioerodible implant of claim 50 wherein the active agent is about 60 percent by weight of the bioerodible implant.

52. The bioerodible implant of claim 44 wherein said hydrophilic end group is carboxyl, hydroxyl, polyethylene glycol, or a combination thereof.

53. The bioerodible implant of claim 44 wherein said hydrophobic end group is an alkyl ester or aromatic ester.

54. The bioerodible implant of claim 44 wherein the mixture has a weight ratio of hydrophilic end group PLGA to hydrophobic end group PLGA of about 3:1.

55. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vivo* in rabbit eye in which less than about 15 percent of the active agent is released about one day after implantation of the bioerodible implant.

56. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vivo* in rabbit eye in which less than about 20 percent of the active agent is released about three days after implantation of the bioerodible implant.

57. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vivo* in rabbit eye in which greater than about 65 percent of the active agent is released about 21 days after implantation of the bioerodible implant.

58. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vivo* in rabbit eye in which greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant.

59. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vivo* in rabbit eye in which greater than about 95 percent of the active agent is released about 35 days after implantation of the bioerodible implant.

60. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vivo* in rabbit eye in which less than about 15 percent of the active agent is released about one day after implantation of the bioerodible

implant and greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant.

61. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vitro* in which less than about 5 percent of the active agent is released about one day after implantation of the bioerodible implant.

62. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vitro* in which less than about 7 percent of the active agent is released about four days after implantation of the bioerodible implant.

63. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vitro* in which greater than about 70 percent of the active agent is released about 21 days after implantation of the bioerodible implant.

64. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vitro* in which greater than about 85 percent of the active agent is released about 28 days after implantation of the bioerodible implant.

65. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vitro* in which greater than about 95 percent of the active agent is released about 35 days after implantation of the bioerodible implant

66. The bioerodible implant of claim 44 wherein the bioerodible implant has a cumulative release profile *in vitro* in which less than about 5 percent of the active agent is released about one day after implantation of the bioerodible implant and in which greater than about 85 percent of the active agent is released about 28 days after implantation of the bioerodible implant.

67. The bioerodible implant of claim 44 wherein the bioerodible implant is formed by an extrusion method.

68. The bioerodible implant of claim 44 wherein the ocular region is selected from the group consisting of the anterior chamber, the posterior chamber, the vitreous cavity, the choroid, the suprachoroidal space, the conjunctiva, the subconjunctival space, the episcleral space, the intracorneal space, the epicorneal space, the sclera, the pars plana, surgically-induced avascular regions, the macula, and the retina.

69. The bioerodible implant of claim 44 wherein the ocular region is the vitreous cavity.

70. A method for treating a medical condition of the eye in a subject comprising implanting into an ocular region of the subject a bioerodible implant of any one of claims 1-69 and delivering a therapeutic amount of an active agent to the ocular region.

71. The method of claim 70, wherein the subject is human.

72. The method of claim 70, wherein the medical condition of the eye is selected from the group consisting of uveitis, macular edema, macular degeneration, retinal detachment, ocular tumors, fungal infections, viral infections, multifocal choroiditis, diabetic retinopathy, proliferative vitreoretinopathy (PVR), sympathetic opthalmia, Vogt Koyanagi-Harada (VKH) syndrome, histoplasmosis, uveal diffusion, and vascular occlusion.

73. The method of claim 70 wherein the step of implantation of the bioerodible implant results in an approximately 10-fold less concentration of the active agent *in vivo* in rabbit aqueous humor than in rabbit vitreous humor.

74. The method of claim 70 further comprising the step of varying the size of the bioerodible implant to modify the therapeutic amount of active agent in the ocular region.

75. A bioerodible implant for treating a medical condition of the eye comprising an active agent dispersed within a biodegradable polymer matrix, wherein the bioerodible implant has an *in vivo* in rabbit eye cumulative release profile in which less than about 15 percent of the active agent is released about one day after implantation of the bioerodible implant and greater than about 80 percent of the active agent is released about 28 days after implantation of the bioerodible implant.

76. The bioerodible implant of claim 75 wherein the active agent is selected from the group consisting of ace-inhibitors, endogenous cytokines, agents that influence basement membrane, agents that influence the growth of endothelial cells, adrenergic agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, anti-inflammatory agents, antihypertensives, pressors, antibacterials, antivirals, antifungals, antiprotozoals, anti-infective agents, antitumor agents, antimetabolites, and antiangiogenic agents.

77. The bioerodible implant of claim 75 wherein the active agent comprises an anti-inflammatory agent or any derivative thereof.

78. The bioerodible implant of claim 75 wherein the active agent comprises a steroidal anti-inflammatory agent or any derivative thereof.

79. The bioerodible implant of claim 78 wherein the active agent is selected from the group consisting of cortisone, dexamethasone, fluocinolone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and any derivative thereof.

80. The bioerodible implant of claim 78 wherein the active agent comprises dexamethasone.

81. The bioerodible implant of claim 75 wherein the active agent is about 10 to about 90 percent by weight of the bioerodible implant.

82. The bioerodible implant of claim 81 wherein the active agent is about 60 percent by weight of the bioerodible implant.

83. The bioerodible implant of claim 75 wherein biodegradable polymer matrix comprises a mixture of hydrophilic end group PLGA and hydrophobic end group PLGA.

84. The bioerodible implant of claim 83 wherein said hydrophilic end group is carboxyl, hydroxyl, polyethylene glycol, or a combination thereof.

85. The bioerodible implant of claim 83 wherein said hydrophobic end group is an alkyl ester or aromatic ester.

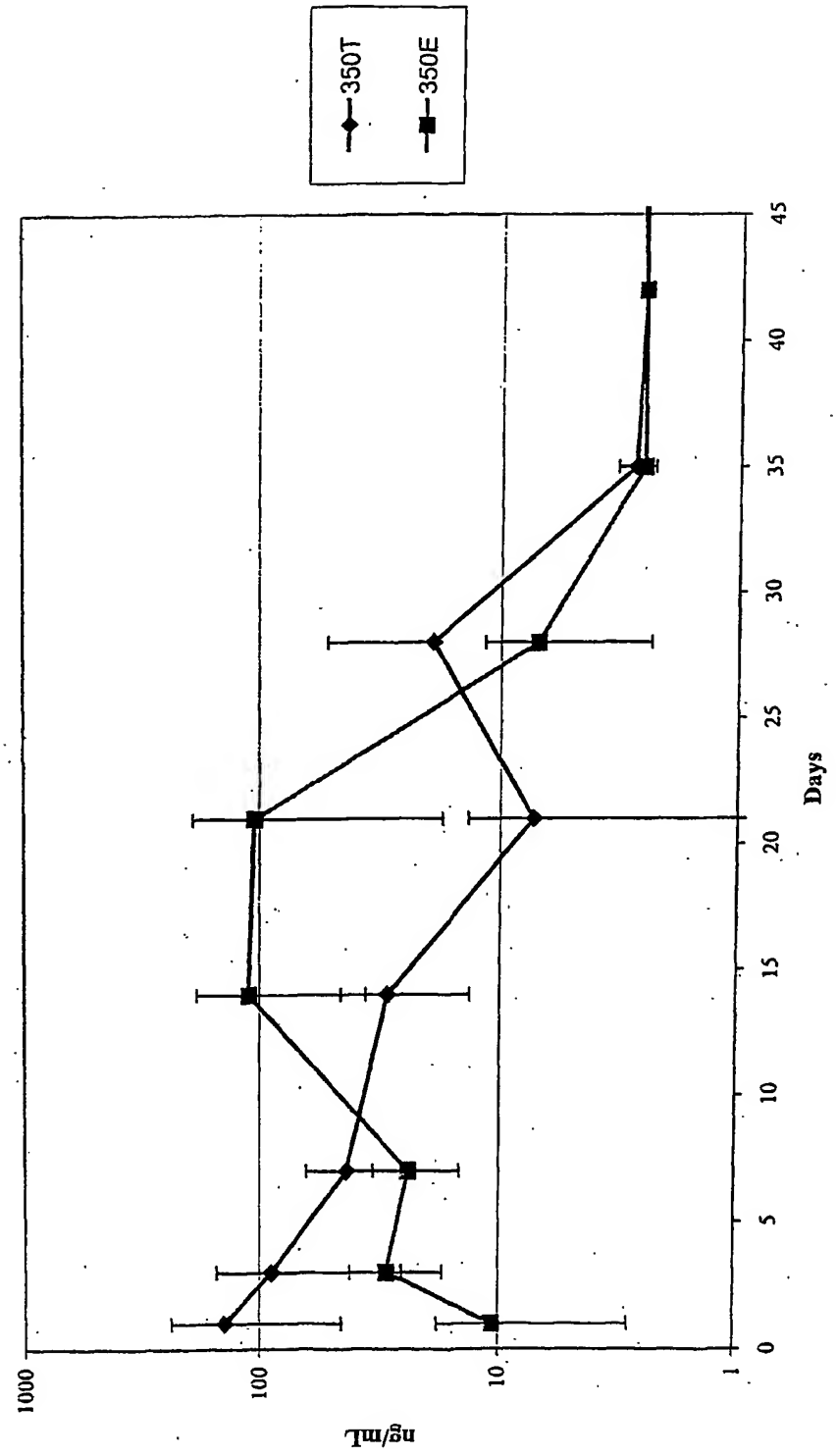
86. The bioerodible implant of claim 83 wherein the mixture has a weight ratio of hydrophilic end group PLGA to hydrophobic end group PLGA of about 3:1.

87. The bioerodible implant of claim 75 wherein the implant is sized for implantation in an ocular region.

88. The bioerodible implant of claim 87 wherein the ocular region is selected from the group consisting of the anterior chamber, the posterior chamber, the vitreous cavity, the choroid, the suprachoroidal space, the conjunctiva, the subconjunctival space, the episcleral space, the intracorneal space, the epicorneal space, the sclera, the pars plana, surgically-induced avascular regions, the macula, and the retina.

89. The bioerodible implant of claim 87 wherein the ocular region is the vitreous cavity.

Figure 1



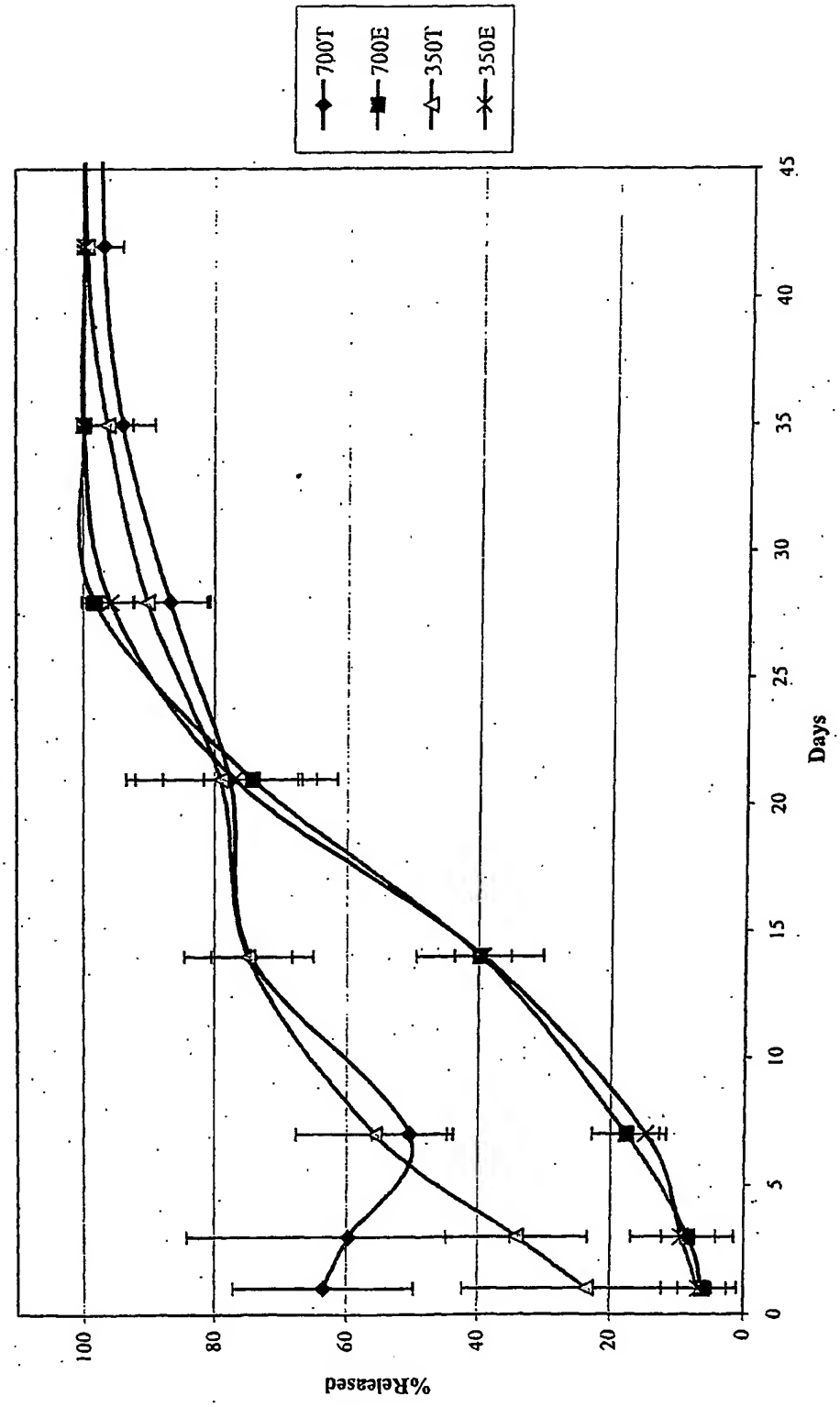

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Figure 2

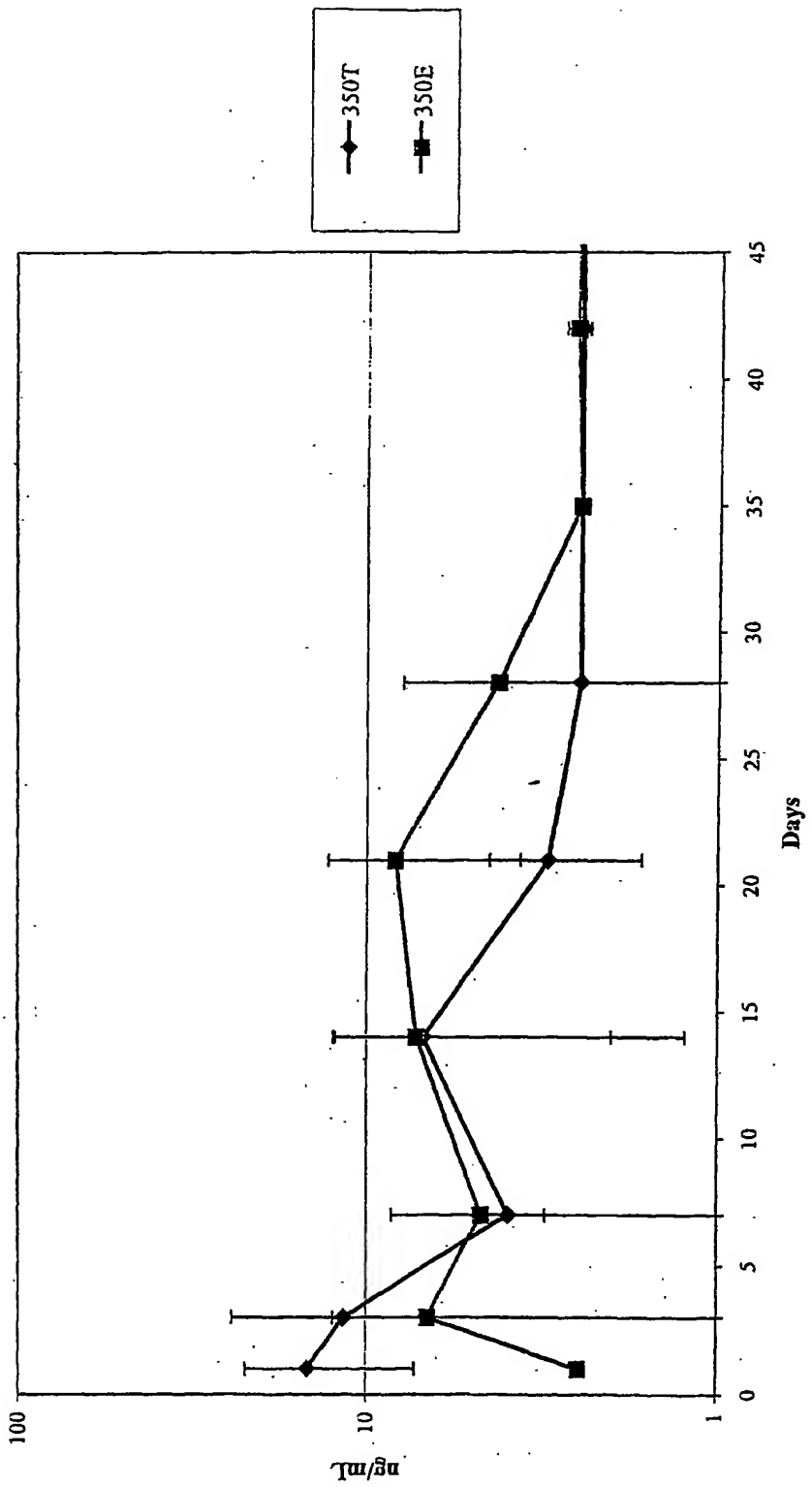


Figure 3

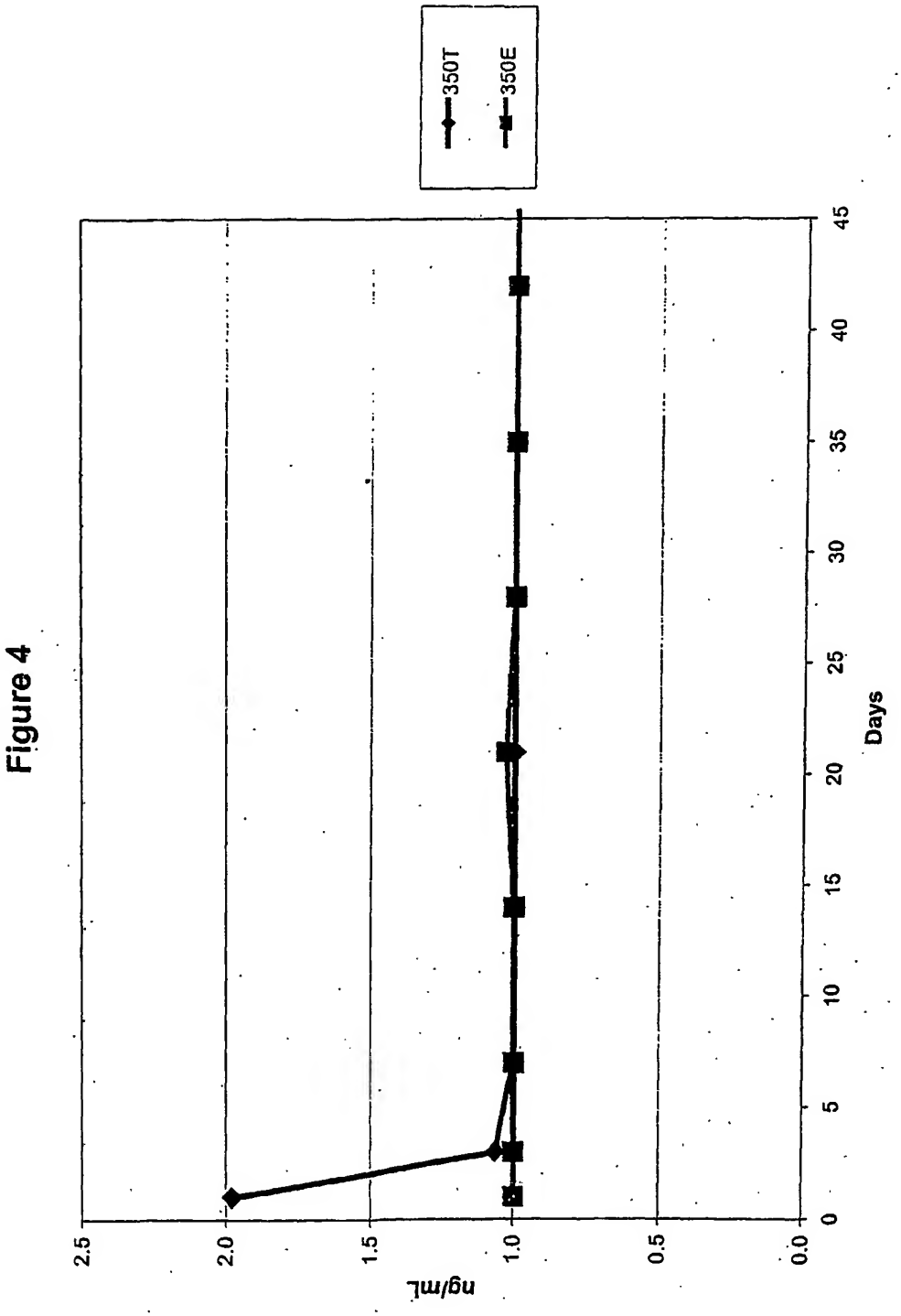


Figure 4

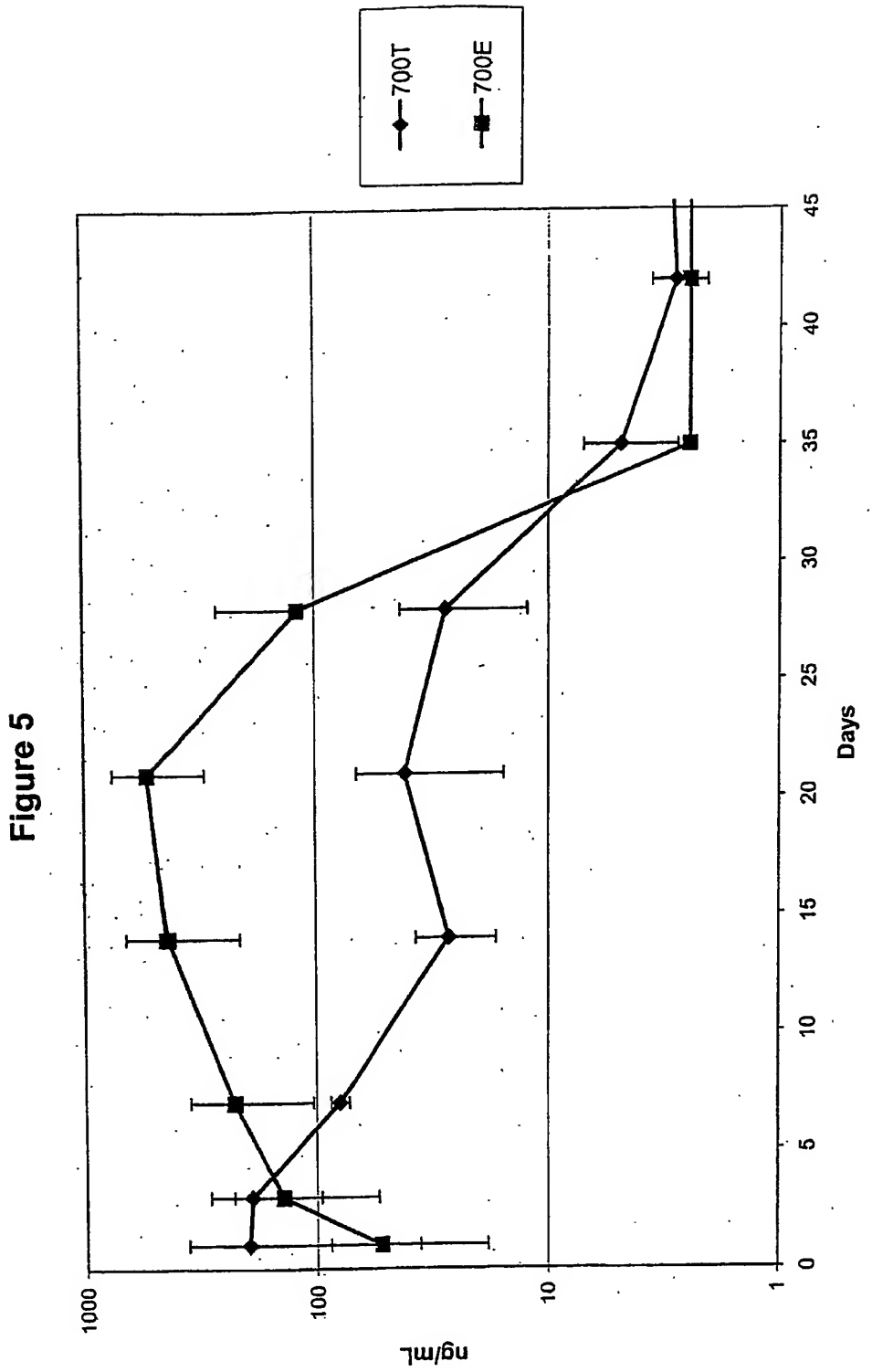
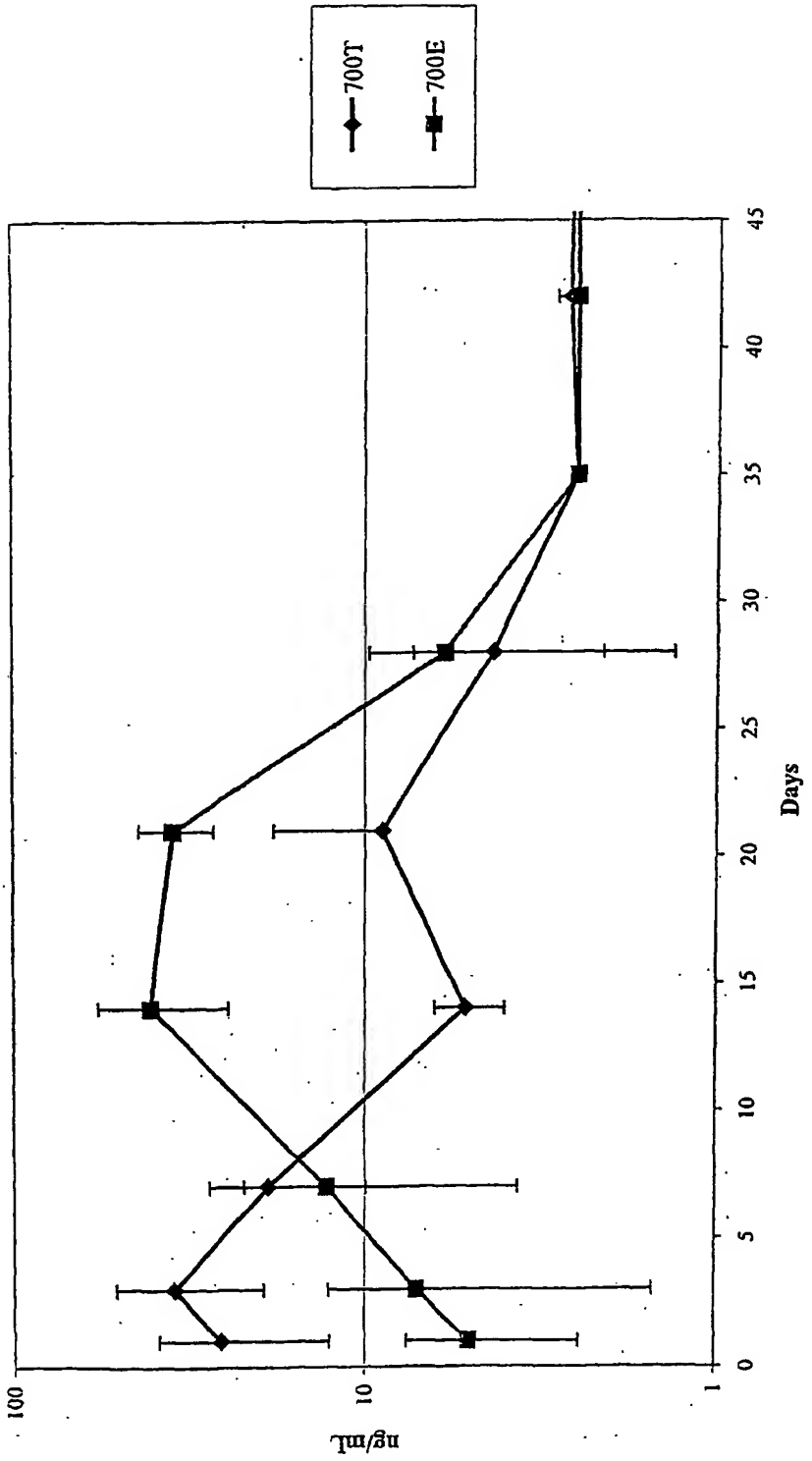


Figure 5



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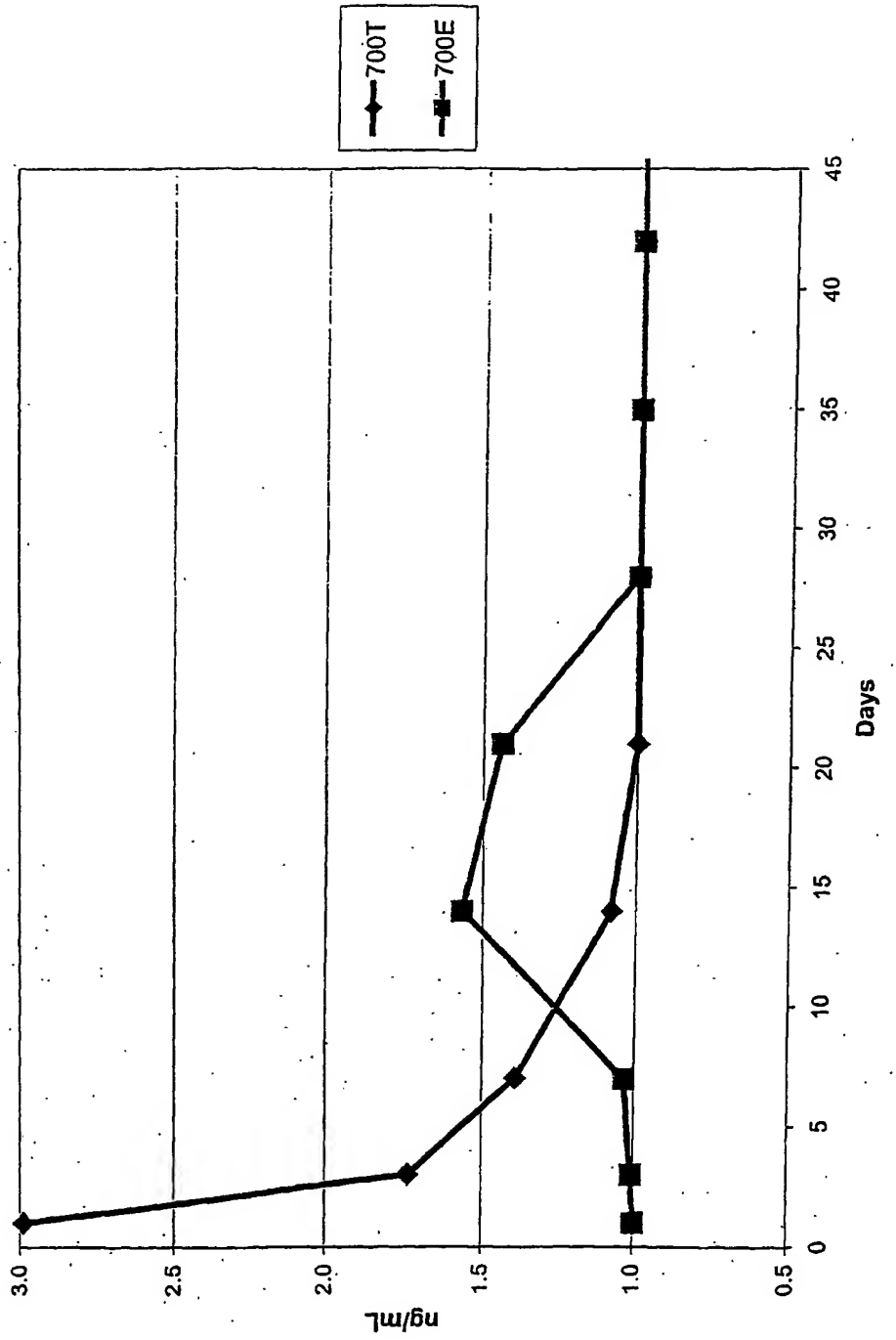
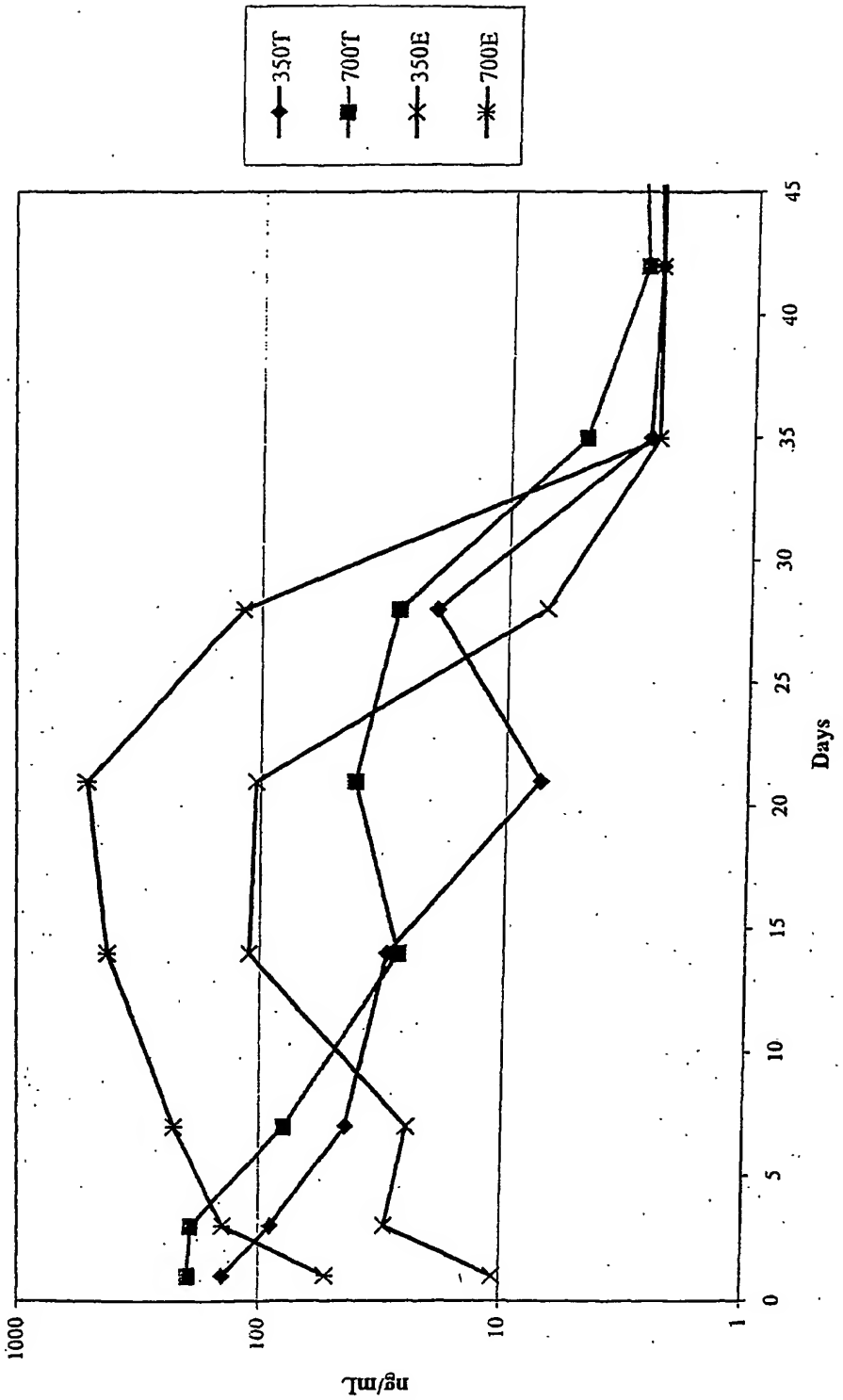


Figure 7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25
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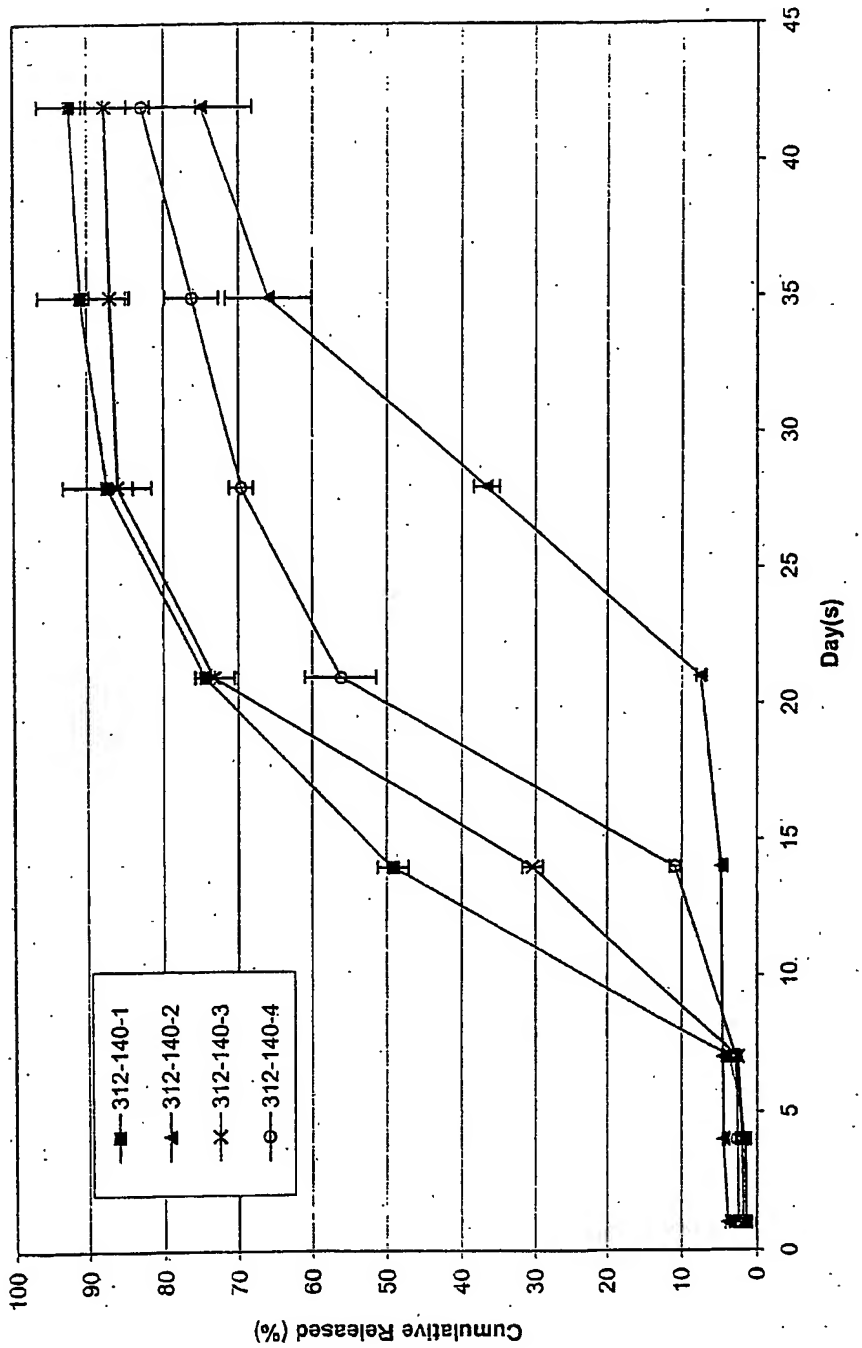
Days

Figure 8

FIGURE 9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Day(s)
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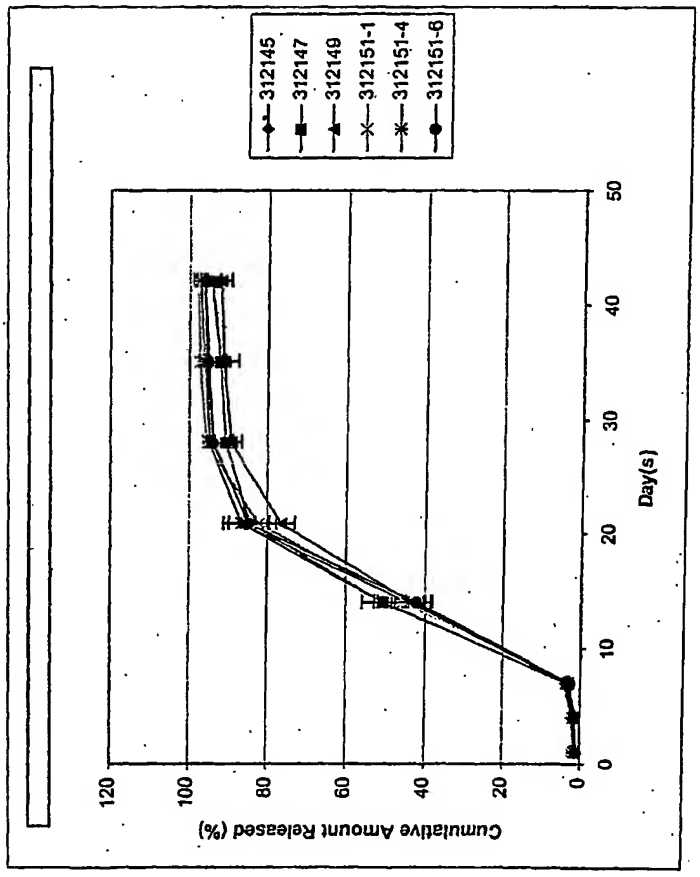
312-140-2
312-140-3
312-140-4

FIGURE 10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312147
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312151-4
312151-6
Cumulative Amount Released (%)
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Day(s)
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20
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40
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(71) Applicant *(for all designated States except US)*: **ALLERGAN, INC.** [US/US]; 2525 Dupont Drive, Irvine, CA 92612 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **NIVAGGIOLI, Thierry** [US/US]; 12020 Green Hills Court, Los Altos Hills, CA 94022 (US). **PENG, Lin** [US/US]; 1177 Amarillo Avenue, #1, Palo Alto, CA 94303 (US). **CHOU, David** [US/US]; 2918 Kipling Street, Palo Alto, CA 94306 (US). **WEBER, David** [US/US]; 21 Estrella Place, Danville, CA 94526 (US).

(74) Agents: **DONOVAN, Stephen** et al.; c/o Allergan, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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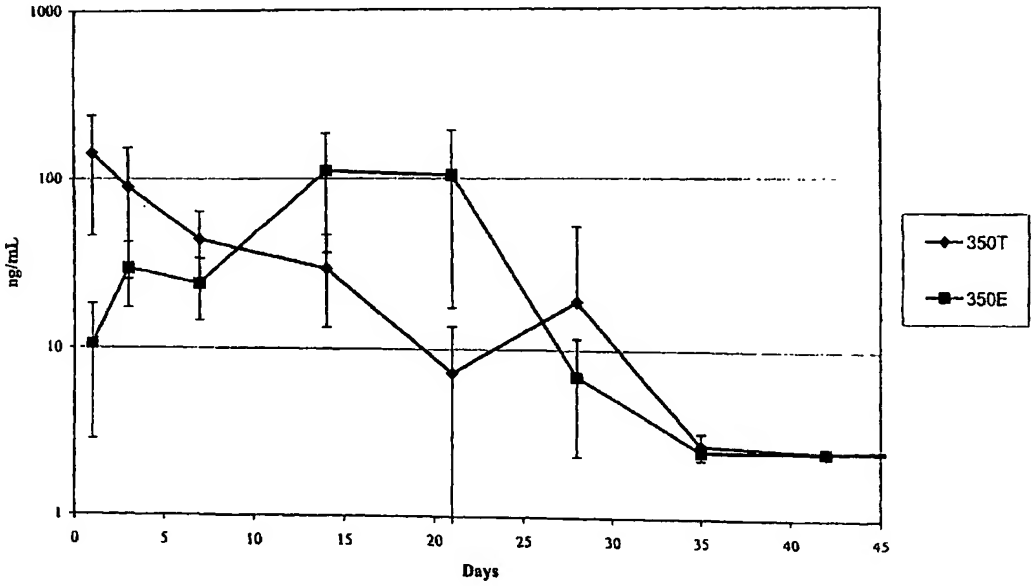
Published:
— *with international search report*

(88) Date of publication of the international search report:
4 November 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BIODEGRADABLE OCULAR IMPLANT



(57) Abstract: The invention provides biodegradable implants sized for implantation in an ocular region and methods for treating medical conditions of the eye. The implants are formed from a mixture of hydrophilic end and hydrophobic end PLGA, and deliver active agents into an ocular region without a high burst release.

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INTERNATIONAL SEARCH REPORT

Int[illegible]plication No
PCT/US2004/000351

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 052 916 A (ALZA CORP) 2 June 1982 (1982-06-02) examples -----	1-4, 7-12, 16-18, 23-30, 34-36, 41-43, 70-77
X	EP 0 992 244 A (SANTEN PHARMA CO LTD) 12 April 2000 (2000-04-12) examples ----- -/--	1-3, 7-13,16, 18, 23-31, 34,36, 41-43, 70-78, 81,87-89

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 June 2004	02.07.04

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/US2004/000351

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

tional application No.
PCT/US2004/000351

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 70-74 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/000351

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